Patterns of clinicopathological features and outcome in epithelial ovarian cancer 1 patients: 35 years of prospectively collected data.

Title: Patterns of clinicopathological features and outcome in epithelial ovarian cancer patients: 35 years of prospectively collected data.

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Shortened Title: Patterns in ovarian cancer outcome over time.

ABSTRACT

Objective: Investigate the clinical landscape of ovarian carcinoma(OC) over time.

Design: Register-based prospectively collected data.

Setting: South-East Scotland

Sample: 2805 OC patients diagnosed 1981-2015.

Methods: Survival times were visualised using the Kaplan-Meier method; median survival, 5-year survival probabilities and associated restricted mean survival time analyses were used to quantify survival differences

Main Outcome Measures: Disease-specific survival.

Results: Significant increase in disease-specific survival(DSS) from 1981-1985 to 2011-2015 was observed (median 1.73 vs 4.23 years, p<0.0001). Corresponding increase in progression-free survival(PFS) was not statistically significant (median 1.22 vs 1.58 years, p=0.2568). An increase in the proportion of cases with low residual disease volume (RD) (<2cm RD) following debulking was observed (54.0% vs 87.7%, p<0.0001). The proportion of high grade serous (HGS) cases increased (p<0.0001), while endometrioid and mucinous cases decreased (p=0.0005 and p=0.0002). Increases in stage IV HGSOC incidence (p=0.0009) and stage IV HGSOC DSS (p=0.0122) were observed. Increasing median age at diagnosis correlated with increasing Eastern Cooperative Oncology Group Performance Status (ECOG PS) over time (r=0.86).

Conclusions: OC DSS has improved over the last 35 years; PFS has not significantly increased, highlighting that improvement in outcome has been limited to extending post-relapse survival. Distribution of stage at diagnosis, histological subtype and RD following debulking have changed over time, reflecting evolution in tumour classification, staging and optimal debulking definitions (from low RD to minimal or zero RD). Histology, stage, RD and ECOG PS remain reliable outcome predictors. Increasing median age at diagnosis and ECOG PS indicates demographic shifts in the clinical population.

Keywords: ovarian cancer, survival, prognosis, diagnosis.

Tweetable Abstract: Significant improvement in ovarian carcinoma survival has been seen over time. Most of this improvement is due to an extension of survival following disease relapse

INTRODUCTION

With over 290, 000 new diagnoses and 180, 000 deaths per year worldwide, ovarian cancer is the most lethal of all gynaecological malignancies[1]. This is attributed, in part, to the high frequency at which these malignancies are diagnosed at advanced stage, which represents a major clinical challenge. For these advanced stage cases, the 5-year survival rate remains poor at under 30%[2].

It is now recognised that ovarian carcinoma (OC) - which represents around 90% of ovarian cancer cases - is a collection of discrete diseases, the five main histotypes of which are high grade serous (HGS), endometrioid, clear cell (CC), mucinous and low grade serous (LGS) OC[3]. These histotypes display distinct clinical characteristics, with differing intrinsic chemosensitivity, typical stage at diagnosis and overall survival outcome[4]. Moreover, these histotypes are now known to arise from distinct gynaecological sites[5-9].

Despite intensive research efforts to find further therapeutic options, the standard-of-care for OC has largely remained static in recent decades, comprising maximal cytoreductive debulking surgery followed by platinum based chemotherapy, frequently in combination with taxanes[10]. In recent years, the use of anti-angiogenic treatments and PARP inhibitors has been integrated into routine practice, with several trials demonstrating prolonged progression-free survival largely in the relapse disease setting[11-16]. Recognition of the biologically distinct histotypes within OC has highlighted the need for identifying new histotype-specific therapeutic treatments[17] and has led to rationally designed histotype-specific trials of biological agents[18, 19].

It is well established that disease stage at diagnosis, patient age and ECOG performance status (ECOG PS)[20-23] are associated with differential survival outcomes in OC patients; moreover, optimal surgical cytoreduction has emerged as one of the most important determinants of outcome[24-26]. The definition of optimal cytoreduction has evolved alongside our understanding of OC as a disease entity[27-31], with the goal of surgery evolving from <2cm maximal dimension of the largest residual disease (RD) lesion to minimal RD (<0.5cm) to the current objective of achieving no visible RD[29-32].

Here, we investigate the changing clinical landscape of ovarian carcinoma patients from South-East Scotland (population 1.4 million) over the last 35 years (1981 – 2015) using data retrieved from The Edinburgh Ovarian Cancer Database.

METHODS

Cases

Cases were identified using the Edinburgh Ovarian Cancer Database; patient demographics and survival data, prospectively collected as part of routine clinical care, were retrieved from the database. No independent ethical approval for this study was required, as determined by the South East Scotland Research Ethics Service.

All pathologically confirmed epithelial OC diagnoses of serous, mucinous, endometrioid or clear cell histological type between 1981-2015 were included (Figure S1), including cases recorded as primary fallopian tube or primary peritoneal carcinoma, representing the vast majority of OC cases in the region (for example, cases treated solely within private practice will not have attended at the Edinburgh Cancer Centre). All other histotypes were excluded. Historically diagnosed grade II serous carcinomas (n=189) were included with documented grade III serous carcinomas (n=1010) and HGSOCs (n=554). Well differentiated serous (n=107) OCs were included alongside contemporary diagnoses of LGSOC (n=10). Serous carcinomas with unknown grade or variable differentiation were excluded (n=96). 51.0% of cases represented either contemporary diagnoses (2010 onwards), or cases where histotype has been confirmed by contemporary pathology review by an expert gynaecological pathologist (CSH)[33-39].

Demographics

Patients were classified into 5-year cohorts using date of pathologically confirmed OC diagnosis (1981 – 1985, 1986 – 1990, 1991 – 1995, 1996 – 2000, 2001 – 2005, 2006 – 2010, 2011 – 2015). Staging information was based on the International Federation of Obstetrics and Gynaecology (FIGO) staging system. Debulking status was classified as <2cm and ≥2cm residual disease (RD). Debulking status could not be resolved beyond <2cm due to the retrospective nature of these data and historic classification of <2cm RD as optimal debulking prior to 2008. ECOG performance status (PS) was categorised discretely from 0 (PS 0) – 4 (PS 4). Due to the low number of cases with PS 4 (n=6), these cases were excluded from PS analysis. 5 distinct cases were excluded from survival analysis (4 from disease-specific survival (DSS) and 4 from progression-free survival (PFS) analysis) due to missing outcome data.

Statistical analysis

DSS was evaluated as time from date of diagnosis to disease-specific death. Deaths from other causes were censored. PFS was evaluated as time from date of diagnosis to date of OC progression[40], where progression was established by radiologically confirmed progressive disease (PD), CA125 PD or clinical deterioration as determined by the treating physician. Statistical analyses were performed using R 3.6.1. Survival analyses were visualised using the Kaplan-Meier method. Survival statistics are presented with median survival with corresponding 95% confidence intervals (CIs), alongside 5- and 10-year survival rates and statistical comparison by restricted mean survival time analysis. Multivariable analyses were performed using Cox proportional hazards regression models, stratified by RD, histotype and age or PS. Differences in frequency were analysed using the Chi-squared test. $P<0.05$ was considered statistically significant.

RESULTS

2805 patients met the inclusion criteria (Figure S1, Table 1). 51.0% of all cases represented contemporary diagnoses (2010 onwards) or had their histotype confirmed by pathology review: 56.5% HGS; 52.2% LGS; 42.1% endometrioid; 53.2% clear cell; 27.7% mucinous (Table S1).

Outcome of OC across all time periods

Across the whole OC cohort, the median DSS was 3.13 years (95% CI: 2.87 - 3.42) and the median PFS was 1.45 years (95% CI: 1.36 - 1.54). The overall 5-year and 10-year DSS rates were 38.5% (95% CI: 36.6% - 40.5%) and 27.6% (95% CI: 25.8% - 29.6%).

The current 5-year DSS, given by the 2011-2015 estimate, was 45.6% (95% CI: 40.7% - 51.1%). The DSS across the year ranges, inclusive of all histotypes, increased incrementally (Figure 1, Table S2), with cohorts diagnosed after 1995 demonstrating significant increases in median DSS when compared to the 1981-1985 cohort. The greatest improvement was observed in the most contemporary cohort patient group (diagnosed 2011-2015), with a significantly increased median DSS (4.23 years, 95% CI 3.73-5.13 vs 1.73 years, 95% CI: 1.53-2.21 in 1981-1985, $p<0.0001$). Conversely, PFS across the year ranges demonstrated little improvement, with no significant difference between 1981-1985 and 2011-2015 (median PFS 1.22 years, 95% CI: 1.09-1.78 vs 1.58 years, 95% CI: 1.41-1.86, $p=0.2568$) (Figure 2, Table S3). While there was an apparent correlative increase in PFS with increase in DSS across time ($r=0.80$) (Figure S2), the magnitude of PFS increase was slight.

Patterns in clinicopathological features over time

<u>Histotype</u>

An increase in the proportion of HGSOC cases was seen (129 of 223 cases, 57.8% in 1981-1985 vs 373 of 544 cases, 68.6% in 2011-2015, $p<0.0001$ across diagnosis periods) while the proportion of mucinous cases decreased significantly (38 of 223 cases, 17.0% in 1981-1985 vs 44 of 544 cases, 8.1% in 2011-2015, $p=0.0002$ across diagnosis periods). The proportion of endometrioid cases decreased over time (23 of 223 cases, 10.3% in 1981-1985 vs 50 of 544 cases, 9.2% in 2011-2015, $p=0.0005$ across diagnosis periods).

Stage at Diagnosis & RD following debulking

An overall increase in the proportion of Stage IV HGSOC patients was seen over the year ranges (14 of 122 cases, 11.5% in 1981-1985 vs 85 of 317 cases, 26.8% in 2011-2015, p=0.0009). A corresponding decrease in HGSOC patients presenting with Stage I was seen (14 of 122 cases, 11.4% in 1981-1985 vs 16 of 317 cases, 5.0% in 2011-2015, p=0.0293). The proportion of cases with <2cm RD increased greatly in 2011-2015 to 87.7% (vs 54.0% in 1981-1985, p<0.0001).

ECOG Performance Status & Age at Diagnosis

The proportion of PS 0 cases decreased over time (73 of 173 cases, 42.2% in 1981-1985 vs 98 of 451 cases, 21.7% in 2011-2015, p<0.0001), while the proportion of PS 2 cases increased (17 of 173 cases, 9.8% in 1981-1985 vs 95 of 451 cases, 21.1% in 2011-2015, p=0.0016) (table 1). The median age at diagnosis significantly increases across time (57 years in 1981-1985 vs 66 years in 2011-2015, p<0.0001) (Figure 3A). When plotted against the mean PS for each 5-year cohort, a strong correlation can be observed (r=0.86) (Figure 3B), consistent of the overall correlation between age and PS across the cohort (Figure S3).

Associations between histological subtype and outcome

HGSOC demonstrated the lowest 5-year DSS (25.0%, 95% CI: 22.9% - 27.2%) of the histotypes (Figure 2A), while mucinous carcinomas showed the most favourable DSS (5-year survival: 75.0%, 95% CI: 69.9% - 80.4%, p<0.0001 vs HGSOC), followed by LGSOC (5-year survival: 63.8%, 95% CI: 55.2% - 73.8%, p<0.0001 vs HGSOC) and endometrioid OC (5-year survival: 60.0%, 95% CI: 55.1% - 65.4%, p<0.0001 vs HGSOC). Stage-specific analysis revealed markedly poor outcome in mucinous and CC OC diagnoses at advanced stage (FIGO III/IV) (mucinous median DSS: 0.88 years, 95% CI: 0.55 – 1.75, CC median DSS: 0.85 years, 95% CI: 0.65 – 1.34), while LGSOC showed the highest median survival of 6.76 years in this analysis (Figure 2E). Corresponding early stage (Stage I and II) DSS analysis mirrored the results of the overall DSS analysis (Figure 2A).

Associations between other clinicopathologic features and outcome

Low RD volume following surgical debulking, lower PS and earlier stage were all associated with significantly prolonged DSS (Figure 2B, 2C, 2D). Patients with <2cm RD demonstrated

significantly higher median survival (7.33 yrs, 95% CI: 6.46 – 8.80, p<0.0001) than those with ≥2cm of RD (1.46 years, 95% CI: 1.32 – 1.55). Each increase in performance status (reduction in ECOG PS score) saw a significantly increased median survival (Figure 2D, Table S2). PS3 was associated with a median survival of 0.67 years (95% CI: 0.43 – 1.01), while PS0 was associated with a median survival of 5.52 years (95% CI: 4.81 – 6.80) (p<0.0001, PS3 vs PS0). Similarly, Stages I, II and III showed higher DSS compared to Stage IV (p<0.0001 for all) (Figure 2B, Table S2).

Multivariable analysis of disease stage at diagnosis, histotype, time period of diagnosis, RD volume, ECOG PS and age at diagnosis reflected the univariable analyses (Table S4 and S5). Notably, these data highlight an independent association of both age and PS with DSS, despite the observed correlation between these two factors (Figure S3).

Associations between clinicopathological features and outcome over time

Changes in DSS and PFS over the 5-year time periods was investigated in the context of specific clinicopathological features (Table S6, Table S7). HGSOC patients demonstrated an increase in median DSS (1.56yrs, 95% CI: 1.36 – 1.92 in 1981-1985 vs 3.07yrs, 95% CI: 2.70 – 3.73 in 2011-2015, p<0.0001). Stage III and IV patients showed significantly prolonged median DSS from 1981-1985 to 2011-2015: 1.30yrs vs 3.44yrs (p<0.0001) and 1.03yrs vs 2.29yrs (p<0.0001) respectively. Increase in median PFS was not significant in Stage III HGSOC patients (0.98yrs vs 1.26yrs, p = 0.1049), but showed statistical significance in Stage IV HGSOC patients (0.45yrs vs 1.17yrs, p = 0.0003). ECOG PS 1 and PS 2 patients also showed significantly prolonged median DSS from 1981-1985 to 2011-2015: 1.05yrs vs 4.45yrs (p<0.0001) and 0.66yrs vs 2.79yrs (p<0.0001), respectively. Patients with <2cm RD displayed apparent fluctuations in PFS over time, with recent years showing shorter median PFS (Table S7).

Specifically in Stage III and IV HGSOC, median DSS improved from 1981-1985 to 2011-2015: 1.36yrs vs 3.13yrs (p<0.0001) and 1.32yrs to 2.27yrs (p=0.0122) respectively (Table S8). Increase in median PFS across the same period was not significant in Stage III HGSOC (0.95yrs vs 1.25yrs, p = 0.0601) but was statistically significant in Stage IV HGSOC (0.69yrs vs 1.14yrs, p = 0.0003) (Table S9). These data mirror the results from the pan-histotype DSS and PFS analysis for stage across the cohort (Table S6, S7).

DISCUSSION

Main Findings

We have demonstrated and quantified the improvement in the DSS of women with epithelial OC across time at the Edinburgh Cancer Centre. A similar improvement in PFS was not seen. Differences in survival based on histotype, RD volume following debulking, ECOG PS and stage found were consistent with previous research. An increase in advanced stage HGSOC incidence and survival was seen. A strong correlation was found between increasing age at diagnosis and ECOG PS across time, indicating a shift in the clinical demographic towards an older patient population with more frequent co-morbidities.

Strengths and Limitations

Strengths of the study include the large number of cases and the high granularity of the prospectively collected clinical and treatment data; few similarly extensive longitudinal analyses of real-world OC data have been reported to date. Data was collected as part of routine care, almost exclusively by a single individual, optimising consistency. We recognise several limitations of this study. Firstly, criteria for defining progression have changed over time[40], and were heterogeneous across the periods defined in our study. Our samples are therefore subject to varying definitions of progression over time - including CA125 and radiological evidence as well as more subjective clinical assessment. Secondly, contemporary pathology review was not carried out for all cases; lack of review for all LGSOC and high grade endometrioid cases, which have historically been poorly differentiated from HGSOCs, is a particular weakness. Moreover, the mucinous OC group had a lower rate of pathology review or contemporary diagnosis, likely a reflection of the increasing rarity of true primary mucinous OC by modern pathological criteria. However, across the whole of our OC cohort, over half of cases were confirmed by pathology review in previous studies or represented contemporary diagnoses, in contrast to previous investigations performing no such review[41-43], representing a major strength of this study over previous work. Differences in practice between treating physicians and the impact of ascertainment bias also represent potential limitations.

Interpretation

The 5-year DSS rate observed in this study for the 2011-2015 period was 46% (95% CI: 41%-51%); this is consistent with data reported by Siegel et al[2]. A significant improvement was seen from 1981-1985 where the 5-year survival rate was 31%. The median DSS improved

significantly from 1.73 years to 4.23 years. This improvement represents the culmination of changes in management over time, including the movement toward centralised care in centres with specialist expertise, more robust histopathological classification, improvements in disease monitoring such as imaging technology, and the introduction of additional therapeutic options. Most notably, platinum-taxane combination chemotherapy was introduced as standard of care within the study time period, and there has been a paradigm shift toward extensive cytoreductive surgery to maximise the chances of complete first-line macroscopic resection of disease[25, 44], aided by neoadjuvant chemotherapy in some patients.

Despite the significantly prolonged DSS observed over time, observed improvement in PFS time failed to meet statistical significance (Table S3, Figure S2). This suggests that while treatment has improved for recurrent disease, there has been little improvement in preventing or significantly prolonging relapse. This is consistent with the static standard of care for first-line OC treatment. Recent studies of first-line olaparib treatment for HGSOC *BRCA1* or *BRCA2* mutant patients[13] and hormone maintenance for LGSOC patients[45] indicate that the coming years may see an improvement in OC PFS with the routine use of these agents. Notably, however, these regimens will be limited to subsets of patients.

A change in proportions of different histotypes was observed over the last 35 years with significant increases in HGSOC cases and decreases in mucinous and endometrioid cases. It is now recognised that many previously diagnosed high grade endometrioid carcinomas in fact represent variants of HGSOC[46]; this may explain the relative depletion of endometrioid diagnoses over time. Moreover, historic misclassification of metastatic malignancies of the gastrointestinal tract as primary mucinous OC may explain the decline in mucinous cases over time[47, 48]. It is therefore likely that the change in proportions of histotypes observed in this study is, at least in part, a result of a refinement in classification of tumour types.

A significant increase in the proportion of HGSOC patients presenting with Stage IV disease was also observed, alongside a corresponding decrease in Stage I patients. This indicates that despite efforts to increase awareness of OC symptoms, these efforts have thus far failed to increase the proportion of early stage diagnoses. However, median DSS for these cases has increased significantly overall, and for HGSOC patients specifically (Table S9, S4), indicating post-relapse management has improved. It is also feasible that the observed increased incidence and survival in advanced stage cases is a consequence of the Will Rogers

phenomenon[49], whereby advances in diagnostic techniques (such as more sensitive imaging) leads to up-staging of cases who would otherwise have been earlier stage. Certainly, increased ability of contemporary imaging to detect features such as epicardial nodes could account for a significant amount of stage shift over the time cohorts analysed. The improved outcome observed in advanced stage cases within our study is consistent with recent SEER analysis demonstrating improved outcome in this patient group[50].

The proportion of cases with <2cm of RD remained within the 50-60 % range for 1981-2010, showing a large increase to 88% in the 2011-2015 year range. It is likely that the emphasis on optimal debulking surgery for OC patients in recent years, driven by the recognition that complete macroscopic cytoreduction is associated with markedly favourable outcome[31], has led to this increase. Moreover, this may account for decreases in median DSS and PFS seen in in the <2cm RD cohort at later diagnosis periods, as modern efforts to achieve complete macroscopic tumour resection – including radical debulking surgery and introduction of neoadjuvant chemotherapy – has enriched this cohort for poor prognosis cases over time.

Difference in survival between histotypes observed in this study was generally consistent with results of previous studies[46, 51, 52]; LGS and endometrioid histotypes displayed better survival compared to HGSOC. Peres et al.[52] found that mucinous OC displayed favourable survival at early stage, but dismal prognosis when diagnosed at advanced stage. As the majority of mucinous cases were Stage I (196/282=70%), the overall trend for favourable survival seen in this study, across time and within each 5-year cohort, is consistent with data previously reported[52]. Our data shows that early-stage mucinous cases show favourable outcome, while advanced-stage cases perform poorly. CC OC demonstrated poor survival at early stage and advanced stage, consistent with previous reports of intrinsic chemoresistance in CC and mucinous OC[4, 53, 54], highlighting the need for targeted therapies aimed at the underlying biology of these malignancies.

Previous studies have uncovered and emphasised the importance of FIGO stage[55, 56] and extent of RD following debulking[55, 57-59] as prognostic factors in OC. This study confirms the importance of these two factors in OC survival, as well as ECOG PS. While there have been recent reports that ECOG PS is of limited importance[20], we observed a clear delineation in survival based on ECOG PS. Moreover, an adjusted multivariable model indicated an association with survival independent of other clinicopathologic factors.

We observed a significant increase in median patient age across time (57yrs in 1981-1985 vs 66yrs in 2011-2015, $p<0.0001$), reflective of the UK's ageing population. A similar increase was seen on comparing the mean PS of cases across time. We show a correlation between increased ages and PS ($r=0.86$) across time. Multivariable analysis indicated the independent adverse associations of both of these factors on survival (Table S4, Table S5). This is indicative of the shift towards an older and frailer clinical demographic, representing a clinically challenging population characterised by co-morbidities, chemotherapy delays and poorer survival outcome[60].

Collectively, these data shed new light on the shifting clinical landscape of OC management, demonstrating survival improvement across time as management of OC patients has evolved. They also highlight the current areas of greatest unmet clinical need, where new therapeutic options are urgently required to improve outcome.

CONCLUSION

OC survival in South-East Scotland has improved markedly over the last 35 years. Histology, stage, extent of RD and ECOG PS are strongly associated with survival outcome. Advanced stage disease has seen an increase in incidence and survival, both within HGSOC specifically and across all histotypes. Despite this, PFS has not seen a corresponding increase. Recent trials of first-line agents for specific subgroups of OC[13, 45] indicate that improvement may be seen over the coming years in PFS in these groups. However, in order to see a large PFS increase in the overall OC population there is an urgent need for further improvements in first-line management. Advanced stage CC and mucinous OCs represent those patients with greatest unmet need. Moreover, the changing clinical demographic towards an older population with more co-morbidities highlights a growing patient group that represent a greater clinical challenge.

Future work should aim to investigate the impact of recently introduced therapeutic options, such as anti-angiogenic therapies and PARP inhibitors, on outcome in OC. In particular, whether the use of these agents in the first-line setting leads to an improvement in the currently stagnant PFS of OC patients, should be investigated.

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Disclosure of Interests

MM: honoraria from Tesaro, BristolMyersSquibb and Roche. FN: Non-personal interests in AstraZeneca and Tesaro. CG: research funding from AstraZeneca, Aprea, Nucana, Tesaro and Novartis; honoraria/consultancy fees from Roche, AstraZeneca, Tesaro, Nucana, MSD, Clovis, Foundation One, Sierra Oncology and Cor2Ed; named on issued/pending patents relating to predicting treatment response in ovarian cancer beyond the scope of this work. AI, RLH, KH, TR, MC, CB and CSH declare no conflicts of interest.

Contribution to Authorship

Conceptualisation: KH, CG, RLH; Data curation: TR, CB; Formal Analysis: AI, KH, RLH; Methodology: AI, CG, RLH; Resources: FN, MM, CSH, CSH; Supervision: CG, RLH; Visualisation: AI, Writing – original draft: AI, RLH; Writing – review & editing: AI, KH, MC, MM, FN, CSH, CG, RLH.

Details of Ethics Approval

We have been informed by South East Scotland Research Ethics Service that studies in ovarian cancer patients using data obtained as part of routine care do not require NHS ethical review. As such, no independent ethical approval for this study was required.

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		Time period (year of diagnosis) N(%)							P-value
		1981 - 1985	1986 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	2006 - 2010	2011 - 2015	
Total Cases		223	275	374	470	471	448	544	
Histotype	High grade serous	129 (57.8)	153 (55.6)	203 (54.3)	295 (62.8)	315 (66.9)	285 (63.6)	373 (68.6)	P<0.001[a]
	Clear cell	15 (6.7)	27 (9.8)	41 (11)	27 (5.7)	39 (8.3)	47 (10.5)	54 (9.9)	
	Low grade serous	18 (8.1)	14 (5.1)	10 (2.7)	18 (3.8)	17 (3.6)	17 (3.8)	23 (4.2)	
	Mucinous	38 (17)	35 (12.7)	52 (13.9)	51 (10.9)	33 (7)	43 (9.6)	44 (8.1)	
	Endometrioid	23 (10.2)	46 (16.7)	68 (18.2)	79 (16.8)	67 (14.2)	56 (12.5)	50 (9.2)	
FIGO stage at diagnosis	I	49 (22)	77 (28)	83 (22.2)	97 (20.6)	72 (15.3)	87 (19.4)	92 (16.9)	P=0.009[b]
	II	20 (9)	30 (10.9)	41 (11)	52 (11.1)	58 (12.3)	54 (12.1)	61 (11.2)	
	III	119 (53.4)	131 (47.6)	188 (50.3)	231 (49.1)	246 (52.2)	188 (42)	232 (42.6)	
	IV	24 (10.8)	31 (11.3)	47 (12.6)	77 (16.4)	73 (15.5)	77 (17.2)	95 (17.5)	
	NA	11 (4.9)	6 (2.2)	15 (4)	13 (2.8)	22 (4.7)	42 (9.4)	64 (11.8)	
RD following debulk	<2cm	116 (52)	165 (60)	199 (53.2)	236 (50.2)	229 (48.6)	213 (47.5)	342 (62.9)	P<0.001[c]
	≥2cm	99 (44.4)	103 (37.5)	134 (35.8)	176 (37.4)	205 (43.5)	142 (31.7)	48 (8.8)	
	NA	8 (3.6)	7 (2.5)	41 (11)	58 (12.3)	37 (7.9)	93 (20.7)	154 (28.3)	
ECOG performance status	0	73 (32.7)	112 (40.7)	83 (22.2)	102 (21.7)	79 (16.8)	52 (11.6)	98 (18)	P<0.001[d]
	1	73 (32.7)	52 (18.9)	66 (17.6)	86 (18.3)	54 (11.5)	96 (21.4)	218 (40.1)	
	2	17 (7.6)	27 (9.8)	24 (6.4)	41 (8.7)	40 (8.5)	53 (11.8)	95 (17.5)	
	3	10 (4.5)	6 (2.2)	8 (2.1)	19 (4)	20 (4.2)	20 (4.5)	38 (7)	
	4	0 (0)	1 (0.4)	0 (0)	0 (0)	2 (0.4)	1 (0.2)	2 (0.4)	
	NA	50 (22.4)	77 (28)	193 (51.6)	222 (47.2)	276 (58.6)	226 (50.4)	93 (17.1)	
First-line chemotherapy	Single agent platinum	15 (6.7)	59 (21.5)	210 (56.1)	272 (57.9)	193 (41.0)	163 (36.4)	146 (26.8)	P<0.001[e]
	Platinum/ taxane	0 (0)	0 (0)	0 (0)	99 (21.1)	200 (42.5)	196 (43.8)	292 (53.7)	
	Other platinum combination	64 (28.7)	76 (27.6)	33 (8.8)	5 (1.1)	8 (1.7)	28 (6.3)	6 (1.1)	
	Other	65 (29.1)	63 (22.9)	47 (12.6)	1 (0.2)	2 (0.4)	0 (0)	1 (0.2)	
	None	79 (35.4)	77 (28)	84 (22.5)	93 (19.8)	68 (14.4)	61 (13.6)	99 (18.2)	
Neoadjuvant chemotherapy	No	223 (100)	275 (100)	374 (100)	470 (100)	471 (100)	368 (82.1)	333 (61.2)	P<0.001[h]
	Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	80 (17.9)[f]	211 (38.8)[g]	

Table 1: Characteristics of cohort according to year of diagnosis. RD, residual disease; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Obstetrics and Gynaecology; NA, not available. [a]Chi-squared test across all histotypes, 1981-1985 vs 2011-2015. [b]Chi-squared test for stage IV vs stage I/II/III/, 1981-1985 vs 2011-2015. [c]Chi-squared test, <2cm vs ≥2cm, 1981-1985 vs 2011-2015. [d]Chi-squared test, PS 0 vs 1 vs 2 vs 3/4, 1981-1985 vs 2011-2015 [e]Chi-squared test across all regime classes, 1981-1985 vs 2011-2015. [f]35.5% of neoadjuvant cases later achieved complete macroscopic resection, vs 58.8% no macroscopic residual disease in primary debulking cases. [g]32.5% of neoadjuvant cases later achieved complete macroscopic resection, vs 41.7% no macroscopic residual disease in primary debulking cases. [h]Chi-squared test for neoadjuvant status, 1981-1985 vs 2011-2015

Figure legends

Figure 1: Survival rate by year of diagnosis. (a) Disease-specific survival (DSS) (b) Progression-free survival (PFS).

Figure 2: Survival trends by (a) histotype DSS (b) stage DSS (c) debulk DSS (d) ECOG performance value DSS (e) advanced stage (FIGO III/IV) histotype DSS (f) advanced stage (FIGO III/IV) histotype PFS.

Figure 3: (a) Boxplot of median age at diagnosis across time.
(b) Scatterplot of mean ECOG performance status and mean age at diagnosis.

Figure S1: Flow diagram for case inclusion. Confirmed, confirmed by contemporary pathology review; contemporary, contemporary diagnosis (2010 onwards); historic, historic diagnosis.

Figure S2: Scatterplot of median DSS and PFS increase over time. X and Y axis are in 1:1 ratio to reflect relative PFS and DSS improvement.

Figure S3: Boxplot of median age at diagnosis for discrete levels of ECOG performance status.